Remarks

Status of the Application and the Present Response

Claims 1-76 are pending in the application. Claims 34-76 have been withdrawn by the Examiner from further consideration as directed to non-elected inventions. Claims 1-33 are under examination and stand rejected. In addition, the Examiner indicated that claims 9, 10, 12, 13, 19-21, and 29-33 are free of prior art.

With entry of the instant response, claim 10 has been canceled without prejudice. Claim 1 has been amended to specify that the target nucleic acid comprise a polynucleotide that encodes a heterologous polypeptide. Support for the amendment is replete in the specification, e.g., original claim 10; and page 9, line 30. The amendment does not introduce new matter.

The following remarks address the other issues raised in the instant Office Action.

Rejection under 35 U.S.C. § 112 - Written Description

Claims 1, 2, 4-6, and 8-33 were rejected under 35 U.S.C. § 112, first paragraph as failing to comply with the written description requirement. Specifically, the Office Action stated that "promoter solubility responsive promoter" is defined in the subject specification as a promoter element that is induced or repressed in a cell in response to an increased concentration of insoluble protein in the cytoplasm." The Office Action then noted that "the solubility responsive promoter of the claims encompasses a large and divergent genus of nucleic acid molecules consisting of any and all prokaryotic, eukaryotic or viral promoters that repond to an increased concentration of insoluble promoter in the cytoplasm of a cell." The Office Action further suggested that "all the species promoters disclosed" in the subject specification are "endogenous to a single prokaryotic organism, yet the claims encompass solubility responsive promoters from all other prokaryotic and eukaryotic cells, all species of organism." The Office Action concluded that "the structurally defined solubility responsive promoters disclosed in the instant application are not representative of the entire genus of solubility responsive promoters." In addition, the Office Action noted that "only the described promoters

comprising the sequences" specifically set forth in the subject specification meet the written description requirement. Applicants respectfully traverse this rejection for the reasons stated below.

A. The subject invention is not directed to protein solubility responsive promoters

First, all the claims currently being rejected are original claims that were present when the application was filed. According to the MPEP, § 2163-I-A, "[t]here is a strong presumption that an adequate written description of the claimed invention is present when the application is filed." The MPEP noted that the issue of lack of adequate written description may arise even for an original claim. However, the MPEP specifically limits such a case to situations "if the claims require *an essential or critical feature* which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art" (MPEP, § 2163-I-A, at page 2100-160; emphasis added). Consistently, when courts find written description problem for original claims, it is because the disclosure does not provide adequate description of certain essential or critical features of the invention being claimed. In biotechnology-related cases of the Court of Appeal for the Federal Circuit that address the written description requirement, the inventions at issue are usually directed to a genus of composition of matters (e.g., chemical compounds, polypeptides, or polynucleotides). In these cases, the composition of matters of which written description is at issue (e.g., nucleotide sequences, amino acid sequences, or compound structures) is the very subject matter being claimed, i.e., essential and critical to the claimed invention.

The instant rejection appears to have been made on an incorrect assumption that the subject invention is directed to protein solubility responsive promoters per se. However, this is certainly not the case. Rather, the claimed invention is directed to host cells harboring a solubility reporter construct and an exogenous polypeptide-encoding polynucleotide (e.g., claims 1-33), and to methods of using such host cell to determine solubility of the target polypeptide (e.g., claims 37-55). The claims are not directed to protein solubility responsive promoters or solubility responsive genes

per se. Patentability of the claimed invention is predicated on the novel concept of employing a protein solubility reporter construct to determine solubility of a polypeptide encoded by an exogenous polynucleotide in the host cell. It does not reside on the solubility responsive promoter, the host cell itself (i.e., cell not harboring the solubility reporter construct and the target nucleic acid), or the target polypeptide.

Just like that of the host cell itself or the target polypeptide, the exact nature of the solubility responsive promoter to be used is not essential or critical to the claimed invention. The law of written description does not require Applicants to disclose representative members of all possible species for these features of the claimed invention. Otherwise, in order to satisfy the written description requirement, Applicants will also have to disclose representative members from all possible species for the other elements recited in the claims, e.g., the host cell, the target polypeptide, or the reporter gene. Such a requirement would surely represent a novel, unreasonable and unwarranted extrapolation of the law.

B. Analogy to a hypothetic example

The impropriety of the instant written description rejection can be further illustrated with a hypothetic invention that claims a novel process for manufacturing furniture with wood. For instance, the invention exemplifies the claimed process with two sources of wood (e.g., pine and oak) and two kinds of furniture (e.g., dinner table and coffee table). Patentability of the claim resides on the novel process, not the type of wood being used or the kind of furniture being manufactured. Because the claim is not directed to the wood or the furniture per se, the exact nature of the wood being used or furniture being produced is not essential or critical to the claimed invention. In such a case, there is no doubt that one of ordinary skill in the art would reasonably conclude that the inventors are in possession of the claimed novel process regardless of the source of wood used or the kind of furniture manufactured.

It is readily clear that, in this hypothetic case, it would be neither necessary nor realistic to require the inventor to disclose all possible sources of wood or

all possible kinds of furniture in order to satisfy the written description requirement. It would also be unreasonable to limit the inventor's claim to only the two exemplified sources of wood, pine and oak, or to the two exemplified kinds of furniture, dinning table and coffee table. Otherwise, since the nature of the wood or the furniture is non-essential to the claimed manufacturing process, a potential infringer can easily circumvent the claim by using a different kind of wood or manufacturing a different kind of furniture. A claim scope so limited would be almost worthless.

As noted above, Applicants' invention does not reside on any specific protein solubility responsive promoter. Instead, it is the concept of employing a protein solubility responsive promoter to determine solubility of a target polypeptide that lie at the center of Applicants' presently claimed invention. Thus, for precisely the same reason as that illustrated in the hypothetic case, the written description requirement does not and should not require the present inventors to disclose representative members of protein solubility responsive promoters from all possible species. Similarly, Applicants' invention should not be limited to the specific promoters or host cell species exemplified in the specification. Just like the non-essential features of wood and furniture in the hypothetic case, the exact nature of the specific promoter or host cell itself to be employed is not essential to the claimed invention. If Applicants are only entitled to the specific solubility responsive promoters or host cell species exemplified in the specification, one can easily avoid infringement of subject invention by using a solubility promoter and/or host cell that are not specifically enumerated in the subject specification.

C. The specification contains adequate description of the claimed invention

As acknowledged in the Office Action, to determine whether the written description requirement is satisfied, the fundamental factual inquiry is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as claimed (Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 19 USPQ2d 1111 (Fed. Cir. 1991; and MPEP § 2163-I). In the instant case, the claimed invention is directed to novel methods and compositions

(e.g., host cells) for employing a solubility reporter construct to determine or analyze solubility-related characteristics of an exogenous target polypeptide (e.g., claims 37-55). As detailed below, the subject specification undoubtedly satisfied the written description requirement.

The specification has disclosed in great detail how to use a solubility responsive gene promoter to monitor solubility of a target polypeptide in a host, as well as a number of solubility responsive promoters that can be used to practice the claimed inventions. For example, with respect to protein solubility responsive gene promoters, the subject specification disclosed that the protein solubility responsive promoter can be a prokaryotic or a eukaryotic promoter. Other than disclosing specific bacterial protein solubility responsive promoters (e.g., promoters from E. coli genes), the specification also disclosed that there are many eukaryotic heat shock and other stress-induced genes that are well known in the art (pages 17, line 24 to page 18, line 28). In addition, the specification teaches how to identify potential solubility responsive promoters from various eukaryotic cells that can be employed to practice the subject invention, e.g., from a number of different yeast cells (page 18, line 30 to page 19, line 20).

In addition to the protein solubility responsive promoters that can be employed in the claimed invention, the specification also provides detailed description of solubility reporter gene constructs (e.g., pages 19-22) and suitable host cells (e.g., pages 18-19). The specification further discloses methods for delivering the reporter construct into the host cell (e.g., page 22, lines 10-16), methods for detecting and quantitating reporter expression (e.g., page 20), and methods for measuring the amount of soluble or insoluble target protein (e.g., page 24, lines 6-27).

Reduction to practice of the claimed invention is demonstrated by the various examples provided in the specification. For instance, the specification exemplifies the claimed invention by using a host cell harboring a solubility reporter construct to test target proteins with pre-determined expression characteristics (page 36, lines 1-16) or with unknown expression characteristics (page 37, lines 4-21). The

specification further provides an example of using the claimed host cell to identify soluble protein domains (page 37, line 25 to page 38, line 21).

If Applicants' invention is directed to protein solubility responsive genes or promoters *per se*, one might reasonably cast doubt as to whether there is adequate written description of the claimed invention to the extent that it is directed to all possible promoter solubility responsive promoters. However, there is not doubt the present inventors indeed had possession of the presently claimed invention, e.g., host cells harboring a solubility reporter construct and methods to use such host cells to determine solubility of an exogenous target polypeptide. First, while not all host cells or protein solubility responsive promoters have been described in the specification, they are either well known in the art or can be easily identified. In addition, admittedly different host cells and solubility responsive promoters may vary tremendously in terms of their biological and biochemical properties. However, the exact nature of these materials is not essential to practicing the claimed invention, and the concept underlying Applicants' invention is equally applicable to all. Therefore, the skilled artisan would reasonably conclude that Applicants had possession of the claimed invention to the extent that it encompasses other host cells or protein solubility promoters not specifically enumerated in the specification.

For all the reasons stated above, Applicants submit that the subject specification has provided adequate written description for the presently claimed invention. Withdrawal of the instant rejection is therefore respectfully requested.

Rejection under 35 U.S.C. § 102

Claims 1, 5, 8, 11, 14-18, 22-25, and 28 were rejected as allegedly anticipated by Farr et al. (US Patent No. 5,589,337). The Examiner noted that "the disclosure does not define the target polypeptide-expressing nucleic acid in such a way as to exclude endogenous genes" and that the rejection is made "insofar as the claims encompass a target polypeptide-expressing nucleic acid that is endogenous to the host cell."

Applicants appreciate the Examiner's careful reviewing of the claims and the subject disclosure. In response, Applicants have amended claim 1 to make it clear the target nucleic acid comprises a polynucleotide that encodes an exogenous polypeptide. As acknowledged in the Office Action, Farr et al. only discusses endogenous genes that are responsive to stresses. Therefore, the presently amended claim 1, and claims 2-9 and 11-33, which depend from claim 1, are all novel and patentable over Farr et al. Accordingly, withdrawal of the instant rejection is respectfully requested.

Rejection under 35 U.S.C. § 103

Claims 1-9, 11, 14-18, 22-25, and 28 were rejected under 35 U.S.C. § 103(a) as allegedly obvious over Farr et al. in view of Allen et al. (J. Bacteriol. 174: 6938-47, 1992). The Office Action alleged that Farr et al. taught the claimed invention except for the specific solubility responsive genes recited in the rejected claims, that Allen et al. taught the promoter region of the E.coli ibpA gene, and that it would be obvious for one to combine teachings from these two references. The Office Action then concluded that the combined disclosures from the cited art render the claims obvious. Applicants respectfully traverse this rejection.

There are three basic elements that must be met to establish prima facie obviousness. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

In the instant case, a prima facie case of obviousness of the presently claimed invention has not and could not be established. First, the cited references, standing alone or in combination, do not teach or suggest each and every element of the claimed invention. As noted above, Farr et al. did not teach or suggest a host cell harboring a protein solubility reporter construct and a polynucleotide that encodes an exogenous target polypeptide. While Allen et al. might have described heat shock genes

including IbpA, this reference does not remedy the deficiency of Farr et al. Thus, even assuming one might be motivated to combine the teachings of the cited references, he would still not be led to the presently claimed invention.

In addition, there would not have been motivation or suggestion to combine teachings of the cited references and that of any other art that might render the subject invention obvious. This is because Farr et al. expressly taught away from the presently claimed invention. For example, after indicating that preferably the host cell strain should be homologous with the stress promoter, Farr et al. further stated that "the strain should also be wild type for all other genes, *especially stress genes*" (Col. 12, lines 33-41; emphasis added). Thus, Farr et al. explicitly suggest to the readers that their host cell and solubility reporter construct system should not be used with exogenous stress genes.

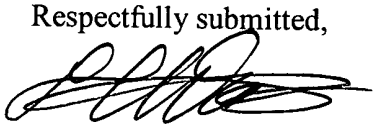
For at least the reasons stated above, Applicants submit that claims 1-9 and 11-33 as presently amended are non-obvious and patentable over the cited art. Accordingly, Applicants respectfully request that the instant rejection be withdrawn.

Conclusion

In view of the foregoing, Applicant believes all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned attorney at 858-812-1539.

Respectfully submitted,



Hugh Wang, Ph.D.
Reg. No. 47,163

GENOMICS INSTITUTE OF THE NOVARTIS RESEARCH FOUNDATION
10675 John Jay Hopkins Drive, Suite E227
San Diego, CA 92121
Tel: (858) 812-1539
Fax: (858) 812-1981